NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

TECHNICAL GRADE

SODIUM XYLENESULFONATE

(CAS NO. 1300-72-7)

IN F344/N RATS AND B6C3F$_1$ MICE

(DERMAL STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

June 1998

NTP TR 464

NIH Publication No. 98-3380

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species, and quantitative risk analyses for humans, require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). The Abstracts and other study information for 2-year studies are available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

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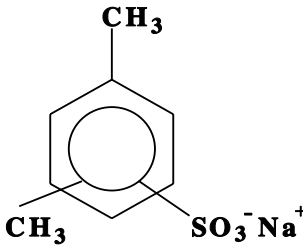
CONTENTS

ABSTRACT



SODIUM XYLENESULFONATE

CAS No. 1300-72-7

Chemical Formula: $(CH_3)_2C_6H_3SO_3^-\ Na^+$ Molecular Weight: 208.2

Synonyms: Benzenesulfonic acid, dimethyl-, sodium salt; sodium dimethylbenzenesulfonate; xylenesulfonic acid, sodium salt
Trade names: Conco SXS; Cyclophil; SXS 30; Eletesol SX 30; Naxonate; Naxonate G; Richonate SXS; Stepanate SXS; Stepanate X; SXS 40; Ultrawet 40SX

Sodium xylenesulfonate is used as a hydrotrope, an organic compound that increases the ability of water to dissolve other molecules. Sodium xylenesulfonate is a component in a variety of widely used shampoos and liquid household detergents where it can constitute up to 10% of the total solution. Because of its widespread use, the potential for human exposure to sodium xylenesulfonate is great. Male and female F344/N rats and B6C3F$_1$ mice were administered sodium xylenesulfonate in water or 50% ethanol dermally for 17 days, 14 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, L5178Y mouse lymphoma cells, and cultured Chinese hamster ovary cells.

17-DAY STUDY IN RATS

Groups of five male and five female rats were administered 300 μL of 0, 5, 15, 44, 133, or 400 mg/mL sodium xylenesulfonate in distilled water by dermal application 5 days per week for 17 days. All rats survived to the end of the study. Final mean body weights and body weight gains of dosed rats were similar to those of the control groups. Dermal applications of 300 μL of 5, 15, 44, 133, and 400 mg/mL delivered average daily doses of approximately 10, 30, 90, 260, and 800 mg sodium xylenesulfonate/kg body weight to males and 13, 40, 120, 330, and 1,030 mg/kg to females. Clinical findings generally involved the skin of dosed animals and included tan or brown skin discoloration and crusty white deposits (presumed to be dried chemical) at the site of application. Neither of these observations were considered significant findings. The relative liver weights of 133 and 400 mg/mL male and female rats were significantly greater than those of the control groups, but the absolute liver weights were not increased and the biological significance of the relative differences in liver weight was unclear. In males and females, the few lesions observed grossly and microscopically were generally attributed to repeated clipping and were not considered related to chemical administration.

17-DAY STUDY IN MICE

Groups of five male and five female mice were administered 100 μL of 0, 5, 15, 44, 133, or

400 mg/mL sodium xylenesulfonate in distilled water by dermal application 5 days per week for 17 days. All mice survived to the end of the study. Final mean body weights and body weight gains of dosed mice were similar to those of the controls. Dermal applications of 5, 15, 44, 133, and 400 mg/mL delivered average daily doses of approximately, 20, 60, 190, 540, and 1,600 mg sodium xylenesulfonate/kg body weight to males and 26, 80, 220, 680, and 2,000 mg/kg to females. Clinical findings included crusty white deposits (presumed to be dried chemical) at the site of application in two 133 mg/mL males and in all 400 mg/mL males and females. The absolute and relative liver weights of 15 and 44 mg/mL males and 400 mg/mL males and females were significantly greater than those of the control groups, but the biological significance of these differences was unclear. The few skin lesions observed grossly and microscopically in males and females were generally attributed to repeated clipping and were not considered related to chemical administration.

14-Week Study in Rats

Groups of 10 male and 10 female rats were administered 300 μL of 0, 5, 15, 44, 133, or 400 mg/mL sodium xylenesulfonate in 50% ethanol by dermal application for 14 weeks. For special hematology and clinical pathology studies, additional groups of 10 male and 10 female rats were administered 0, 5, 15, 44, 133, or 400 mg/mL sodium xylenesulfonate in 50% ethanol by dermal application for 14 weeks. All rats survived to the end of the study. Final mean body weights and body weight gains of dosed male and female rats were similar to those of the control groups. Dermal applications of 5, 15, 44, 133, and 400 mg/mL delivered average daily doses of approximately 6, 20, 60, 170, and 500 mg sodium xylenesulfonate/kg body weight to males and 10, 30, 90, 260, and 800 mg/kg to females. The only notable clinical finding was brown discoloration of the skin at the site of application in dosed animals. Hematology and clinical chemistry parameters of dosed groups of males and females were significantly different from those of the controls in several instances, but these differences were sporadic and did not demonstrate a treatment relationship. The absolute and relative liver weights of males receiving 44, 133, or 400 mg/mL were significantly less than those of the control group, but the biological significance of these differences was unclear, and there were no treatment-related histopathologic effects in the liver. There were no significant differences in liver weights in female rats.

Minimal hyperplasia of the epidermis at the site of application occurred in both male and female rats in the control group as well as most dosed groups. The incidence of epidermal hyperplasia in 400 mg/mL males was possibly chemical related.

14-Week Study in Mice

Groups of 10 male and 10 female mice were administered 100 μL of 0, 5, 15, 44, 133, or 400 mg/mL sodium xylenesulfonate in 50% ethanol by dermal application for 14 weeks. There were no chemical-related deaths. The mean body weight gain of the 400 mg/mL males was significantly greater than that of the control group. Dermal applications of 5, 15, 44, 133, and 400 mg/mL delivered average daily doses of approximately 17, 40, 140, 440, and 1,300 mg sodium xylenesulfonate/kg body weight to males and 20, 60, 170, 530, and 1,630 mg/kg to females. There were no clinical findings related to sodium xylenesulfonate administration.

Epidermal hyperplasia occurred in one 44 mg/mL female, two 133 mg/mL males, five 400 mg/mL males, and four 400 mg/kg females. Hyperplasia of the epidermis in 400 mg/mL males and females was probably related to chemical administration.

Chronic inflammation of the skin occurred primarily in the control groups of males and females. These lesions consisted of mononuclear inflammatory cells in the dermis.

2-Year Study in Rats

Groups of 50 male and 50 female rats were dermally administered 0, 60, 120, or 240 mg sodium xylenesulfonate/kg body weight in 50% ethanol for 104 weeks.

Survival, Body Weights, and Clinical Findings

Survival of dosed males and females was similar to that of the control groups. Mean body weights of dosed males and females were similar to those of the

controls throughout the study. In male groups, there were no clinical findings considered treatment related. In females, clinical findings were limited to irritation at the site of application in one control female, four 120 mg/kg females, and two 240 mg/kg females.

Pathology Findings

There were no neoplasms at any site (including the skin) that were considered treatment related. Low incidences of hyperplasia of the epidermis at the site of application occurred in males in the 60, 120, and 240 mg/kg groups. Low incidences of hyperplasia of the epidermis at the site of application also occurred in females in the 120 and 240 mg/kg groups, and they occurred with a significant positive trend. Low incidences of hyperplasia of the sebaceous gland occurred in control and 60 mg/kg males and in control, 120 mg/kg, and 240 mg/kg females.

2-YEAR STUDY IN MICE

Groups of 50 male and 50 female mice were dermally administered 0, 182, 364, or 727 mg sodium xylenesulfonate/kg body weight in 50% ethanol for 104 to 105 weeks.

Survival, Body Weights, and Clinical Findings

Survival of dosed males and females was similar to that of the control groups. Mean body weights of dosed males and females were generally similar to those of the controls throughout the study; however, the mean body weights of 727 mg/kg females were greater than those of the control group from week 85 to week 97. With the exception of irritation at the site of application in one 364 mg/kg female, there were no clinical findings related to sodium xylenesulfonate administration.

Pathology Findings

There were no neoplasms at any site (including the skin) that were considered treatment related. Hyperplasia of the epidermis occurred in control, 364 mg/kg, and 727 mg/kg males and in control and dosed females. In male mice, the incidences occurred with a significant positive trend. Focal ulceration occurred in one 727 mg/kg male and in one female in each dose group. In males and females from control and dosed groups, the incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatocellular adenoma or carcinoma (combined) were generally higher than those expected by spontaneous occurrence. The incidences of hepatocellular neoplasms in some groups of males and females exceeded the NTP historical control range. Male mice had a pattern of nonneoplastic liver lesions along with silver stained positive helical organisms within the liver which suggests an infection with *Helicobacter hepaticus*. The findings in this study of sodium xylenesulfonate were not considered to have been significantly impacted by the infection with *H. hepaticus* or its associated hepatitis.

GENETIC TOXICOLOGY

Sodium xylenesulfonate was not mutagenic in *Salmonella typhimurium* strain TA98, TA100, TA1535, or TA1537 with or without induced liver S9. Equivocal results were obtained in a mutation assay with mouse lymphoma cells in the presence of induced S9; no evidence of mutagenicity was noted without S9 in this assay. In cytogenetic tests with sodium xylenesulfonate in cultured Chinese hamster ovary cells, significant increases in sister chromatid exchanges were observed in the absence of S9 only, and no increases in chromosomal aberrations were observed with or without S9.

CONCLUSIONS

Under the conditions of these 2-year dermal studies, there was *no evidence of carcinogenic activity** of sodium xylenesulfonate in male or female F344/N rats administered 60, 120, or 240 mg/kg or in male or female B6C3F_1 mice administered 182, 364, or 727 mg/kg.

Increased incidences of epidermal hyperplasia in female rats and male mice may have been related to exposure to sodium xylenesulfonate.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 11.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Sodium Xylenesulfonate

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 60, 120, or 240 mg/kg in 50% ethanol applied dermally	0, 60, 120, or 240 mg/kg in 50% ethanol applied dermally	0, 182, 364, or 727 mg/kg in 50% ethanol applied dermally	0, 182, 364, or 727 mg/kg in 50% ethanol applied dermally
Body weights	Dosed groups similar to control group	Dosed groups similar to control group	Dosed groups similar to control group	Dosed groups similar to control group
2-Year survival rates	7/50, 17/50, 9/50, 10/50	22/50, 16/50, 17/50, 16/50	32/50, 37/50, 39/50, 35/50	31/50, 32/49, 32/50, 36/50
Nonneoplastic effects	None	None	None	None
Neoplastic effects	None	None	None	None
Uncertain findings	None	Skin (site of application): epidermal hyperplasia (1/50, 0/50, 4/50, 5/50)	Skin (site of application): epidermal hyperplasia (1/50, 0/50, 4/50, 5/50)	None
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	No evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Negative with and without S9 in strains TA98, TA100, TA1535, and TA1537			
Mouse lymphoma mutagenicity	Equivocal with S9; negative without S9			
Sister chromatid exchanges				
Cultured Chinese hamster ovary cells *in vitro*:	Negative with S9; positive without S9			
Chromosomal aberrations				
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on technical grade sodium xylenesulfonate on 5 December 1995 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 5 December 1995, the draft Technical Report on the toxicology and carcinogenesis studies of sodium xylenesulfonate received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. A. Radovsky, NIEHS, introduced the toxicology and carcinogenesis studies of sodium xylenesulfonate by discussing the uses of the chemical, describing the experimental design, reporting on survival and body weight effects, and commenting on possible chemical-related nonneoplastic lesions in female rats and male mice. Dr. Radovsky reported that the greater than normal incidence of hepatocellular neoplasms in control and treated male mice could be attributed to infection with *Helicobacter* bacteria. Increased incidences of hepatocellular neoplasms in female mice could not be associated with *Helicobacter* with certainty. The proposed conclusions were *no evidence of carcinogenic activity* of sodium xylenesulfonate in male and female F344/N rats and $B6C3F_1$ mice.

Dr. Carlson, a principal reviewer, agreed with the proposed conclusions. He commented that he would not have used ethanol as vehicle for application of the chemical.

Dr. Goldsworthy, the second principal reviewer, agreed in principle with the proposed conclusions provided there were further clarification and documentation on the role of *Helicobacter* in the mouse liver neoplasm responses. He said that the report needed to better address the response in females and the effects observed in males and females in a comprehensive manner to ensure that the responses are properly interpreted as nontreatment related. Dr. Radovsky responded that several other studies with *Helicobacter* infection were completed and would be reviewed at the next review meeting. Hopefully, firmer conclusions could then be drawn about the association of liver neoplasm response and infection in $B6C3F_1$ mice (Appendix L). Dr. Goldsworthy said the report should more clearly state any potential dose or absorption effects that occurred from changing volumes as well as vehicles from the 17-day studies to the 14-week and 2-year studies, and comment on the relevance of these studies to human exposures. Dr. Radovsky said sodium xylenesulfonate was more soluble in water than in ethanol, but ethanol may have enhanced skin penetration more than water. She said that relevance to human exposure would be speculative on her part.

Dr. Tyson, the third principal reviewer, agreed with the proposed conclusions. He also questioned the use of ethanol as the vehicle noting the association of dermally applied ethanol with induction of mononuclear cell leukemia in F344/N rats.

Dr. W.T. Allaben, NCTR, asked for comment on the poor survival in male rats. Dr. J.R. Bucher, NIEHS, said that male rat survival has declined primarily because of increases in nephropathy, body weight, and incidence of pituitary adenoma. Dr. G.N. Rao, NIEHS, commented that survival of rats is lower when they are individually housed as opposed to group-housed. Dr. J.K. Haseman, NIEHS, said that survival in this study was similar to that in other dermal studies using individual housing. Dr. Ryan asked whether there could be a correlation between mice with *Helicobacter* and those with neoplastic lesions. Dr. J.R. Hailey, NIEHS, said that although not all of the animals had been examined, for those that had, there was a good correlation. Dr. Haseman commented that in the previous study with *Helicobacter*, animals with liver neoplasms had the more severe nonneoplastic lesions that were indicative of the infection. Dr. Goldsworthy thought the infection could be a confounding factor in the interpretation of the liver neoplasms in mice. Dr. Haseman said that while total liver neoplasm rates in this study were above expected rates, they were generally similar across groups, yielding no evidence of a chemical-related increase.

Dr. F. Mirer, Health and Safety Department, United Auto Workers Union, had submitted a statement which, at his request, Dr. L.G. Hart, NIEHS, read into the record. Dr. Mirer opined that the studies were *inadequate* to address the carcinogenicity of

sodium xylenesulfonate in humans. He based his assessment on: (1) not high enough a dose to approach a maximum tolerated dose (MTD); (2) likely poor absorption of such an ionic material through intact skin; and (3) wrong route of exposure to estimate human risk, i.e., inhalation exposure should have been used.

Dr. Carlson moved that the Technical Report on sodium xylenesulfonate be accepted with the revisions discussed and with the conclusions as written for male and female rats and mice, *no evidence of carcinogenic activity*. Dr. Tyson seconded the motion. Dr. Goldsworthy offered an amendment that a statement be added to the Abstract that mice were infected with *Helicobacter*. Dr. Carlson agreed to the amendment, and the amended motion was accepted by six yes votes to one no vote (Dr. Russo). Dr. Allaben asked that a short paragraph be added to the discussion regarding individual animal housing and poor survival.